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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,427	05/10/2001	James Mullin	MUL01-NP001	6770

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UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/853,427	Applicant(s) Mullin et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 26, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *3-12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3-12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed March 26, 2003 (Paper No. 13) in response to the Office Action of January 21, 2003 (Paper No. 8) is acknowledged and has been entered. Claims 3-12 are currently under prosecution.

2. Applicant's reiteration of the prior traverse of the species requirement between sucrose and mannitol is noted. Upon review and reconsideration, the restriction of species requirement is withdrawn.

3. Applicant's election with traverse of the species (c), claims 9 and 12, reduced phosphorylation state of occludin is acknowledged. Upon review and reconsideration, the restriction of species requirement is withdrawn.

Objections

4. Claim 3 is objected to because of an apparent spelling error. In section 3a) it appears that the word"trat" was meant to be "tract". Appropriate correction is required.

5. Claim 11 is objected to because it recites the phrase "altered expression levels a protein selected". Appropriate correction is required.

6. Page 1 is objected to because line 20 recites the phrase "an early stage of a cancerous precancerous condition". Appropriate correction is required.

7. Page 3 is objected to because line 14 recites "Barett's Esophagus". This appears to be a spelling error as a search of the literature did not reveal, other than Applicant's published application, a single hit drawn to Barett's Esophagus. Appropriate correction is required.

8. There appear to be numerous typographical and grammatical errors in the application. Examiner has made an effort to identify these informalities but

applicant must carefully review the specification to identify and indicate where this type of error may be found. Appropriate correction is required.

Specification

9. The specification on page 1 should be amended to reflect the status of the parent provisional application. The following form may be used.

"This application claims benefit to provision application **********, filed **, now abandoned."

Appropriate correction is required.

Declaration

10. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration, in particular, the spelling of Inventor Mullin's name has been altered, See 37 CFR 1.52(c). Further, it does not identify the mailing or post office address of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76. The signatures are undated and it does not identify the city and either state or foreign country of residence of each inventor. The

residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

12. Claims 3-12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by substantial utility.

The disclosed utility for the claimed method is the diagnosis of precancerous conditions of the esophageal mucosa. The utility of the invention appears to be based on the hypothesis that since research has indicated that the tight junctional seal surrounding each epithelial cell in an epithelial tissue is compromised in the process of tumor formation (the physiological implication of this leakiness is that it will compromise the barrier function of the entire epithelial tissue, p. 1, lines 25-34) that precancerous epithelial tight junctions will allow for diffusion of proteins and sugars of the esophagus into the bloodstream (p. 2, lines 5-7), raising their level in serum. The specification further teaches that sucrose is an excellent marker for ulceration-type leakiness in the upper GI tract because it is normally completely broken down on the duodenal microvilli and is normally completely absent from the bloodstream. When there is a defect in the gastric barrier which would enable sucrose to diffuse undegraded into the bloodstream, the diffused sucrose can be subsequently quantitated blood and then urine (p. 14, lines 17-25). However, the

specification states and emphasizes that "it is necessary to **functionally** (emphasis added) verify TJ leakiness in upper GI precancerous states in humans and to determine if proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where a cancerous or precancerous lesion exists. This forms the basis of a noninvasive early detection system for upper GI cancer" (p. 13, lines 17-22). In addition, Clarke et al (Advanced Drug Delivery Reviews, 2000, 41:283-301), IDS item, of which inventor Mullin is the corresponding author, specifically teach on page 295, paragraph bridging columns 1 and 2, that:

"If the association that we and others maintain between epithelial carcinogenesis and TJ leakiness holds true, a *diagnostic* potential **may** (emphasis added) exist. **Should the TJ permeability increase be an early event in epithelial cancer** (emphasis added).....then leakage into the blood stream of luminal fluid proteins characteristic of specific epithelial tissues should also occur early in epithelial tumor development. Ever improving detection technologies **may** (emphasis added) allow for screening these proteins in the bloodstream, detection of which **would then** (emphasis added) indicate the need for further diagnostic testing and thereby provide **potential** (emphasis added) early warning for the development of epithelial cancers."

The specification further teaches a prophetic example, wherein it is taught how to determine whether leakage of proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where precancerous lesion exists (pages 13-15). The reference, published about the time that the instant application was submitted, clearly states that the claimed invention is a potential invention. The specification clearly states that the functional verification of TJ leakiness in upper GI precancerous states in humans is necessary. Applicant admits on the record that additional experimentation is required, therefore, the claimed invention does not

have substantial utility. The specification clearly gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the method of diagnosis.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

14. Claims 3-12 are rejected under 35 USC 112, first paragraph

Specifically, since the claimed invention is not supported by a substantial utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

15. Claims 3-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing a precancerous condition of esophageal mucosa, Barrett's esophageal condition, in a patient comprising the steps of administering to the patient at least one signature carbohydrate, said patient not having ulcerative disease of the gastrointestinal tract nor bleeding therefore, collecting the urine and measuring for the levels of the carbohydrate, wherein the sugar is mannitol or sucrose wherein an increase in the urine levels of the

carbohydrate in the urine of said patient, compared to normal control, is indicative of the precancerous condition, further comprising obtaining a tissue sample from the esophageal mucosa and examining tight junction leakiness of said tissue sample and comparing the TJ leakiness of said tissue sample with that from a control tissue sample wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the precancerous condition, wherein the TJ leakiness is correlated with altered expression levels of a protein selected from the group of alpha Pkc, ZO-1, is correlated with reduced phosphorylation state of occludin.

The specification teaches that the present invention relates to methods of early diagnosis of precancerous conditions in a mammal wherein a biological sample is obtained from a gastrointestinal site to detect the presence of a backleak of signature carbohydrates indicating tight junctional leakiness at an early stage of a precancerous condition (p. 1, lines 14-20). Research has indicated that the tight junctional seal surrounding each epithelial cell in an epithelial tissue is compromised in the process of tumor formation and the physiological implications of this leakiness is that it will compromise the barrier function of the entire epithelial tissue (p. 1, lines 25-34). Precancerous epithelial tight junctions will allow for diffusion of proteins and sugars of the esophagus into the bloodstream (p. 2, lines 5-7). The specification further teaches that tight junctional leakiness in the vicinity of these proteins will allow for their chronic leak into the bloodstream, raising their level in serum. Therefore salivary amylase levels in serum have important diagnostic predictive value for esophageal and gastric precancerous conditions, specifically Barrett's Esophagus, atrophic gastritis and *H. Pylori* infection (p. 3, lines 9-20).

The specification further teaches that sucrose is an excellent marker for ulceration-type leakiness in the upper GI tract because it is normally completely broken down on the duodenal microvilli and is normally completely absent from the bloodstream. When there is a defect in the gastric barrier which would enable undegraded sucrose to diffuse into the bloodstream, the sucrose can be subsequently quantitated in blood and then in urine (p. 14, lines 17-25). The specification exemplifies a prophetic experiment to demonstrate the leakage of luminal salivary amylase and sucrose across the GI barrier in precancerous states in humans (para bridging pages 5-6). The specification describes a prophetic experimental design for the demonstration of the leakage of luminal salivary proteins across the GI barrier in precancerous states in humans. The specification clearly states and emphasizes that "it is necessary to **functionally** (emphasis added) verify TJ leakiness in upper GI precancerous states in humans and to determine if proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where a cancerous or precancerous lesion exists. This forms the basis of a noninvasive early detection system for upper GI cancer" (p. 13, lines 17-22). The specification further teaches a prophetic example, wherein it is taught how to determine whether leakage of proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where precancerous lesion exists (pages 13-15).

One cannot extrapolate the teaching of the specification to the enablement of the claims because Clarke et al (Advanced Drug Delivery Reviews, 2000, 41:283-301), IDS item, of which inventor Mullin is the corresponding author, specifically teach on page 295, paragraph bridging columns 1 and 2, that:

"If the association that we and others maintain between epithelial carcinogenesis and TJ leakiness holds true, a *diagnostic* potential may exist. Should the TJ permeability increase be an early event in epithelial cancer.....then leakage into the blood stream of luminal fluid proteins characteristic of specific epithelial tissues should also occur early in epithelial tumor development. Ever improving detection technologies may allow for screening these proteins in the bloodstream, detection of which would then indicate the need for further diagnostic testing and thereby provide potential early warning for the development of epithelial cancers."

This reference is relevant to the instant rejection since at the time that the application was made, it is clear that Inventor Mullin could not predict that the claimed invention would function as claimed in the absence of further research.

Further, although the specification clearly states that salivary amylase levels in serum have important diagnostic predictive value for esophageal and gastric precancerous conditions, specifically Barrett's Esophagus, atrophic gastritis and H. Pylori infection, a review of the 67 databases of the STN Bioscience cluster did not reveal a single reference to a diagnostic predictive value for amylase in any of the cited precancerous conditions other than the published application of the instant invention. Since it appears to be unknown that amylase is diagnostically predictive for esophageal precancerous conditions, it is not clear whether or not those precancerous conditions are associated with leaky TJ's of whether sucrose or any other signature carbohydrate could be successfully used to diagnose an esophageal precancerous condition. Further, a review of columnar epithelial cells in esophagus (known to be associated with Barrett's esophagus) did not reveal a single reference to increased permeability of TJ leakiness in these cells.

Further, the teaching of Clarke et al reveals that diagnosis of a precancerous condition gives early warning of the development of epithelial cancers. However, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing an cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to diagnosis of a precancerous condition of the esophagus.. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be

confirmed in prospective population trials (p. 2716s, col 2). It appears from the specification and the art of record that no association, much less any validation of that association, of TJ leakiness to precancerous conditions of the esophageal mucosa has been determined. Given the simplicity of the basic assay, that is the assay of sucrose in urine which is well known in the art, one would wonder why the claimed assay has apparently not been done. One would further wonder, if it were to be found that precancerous patients were positive on the sucrose urine assay, why esophageal samples from those patients were not taken and analyzed using techniques that are conventional in the art to provide a nexus between the urine sucrose and precancerous states that might at some time be useful for diagnosis. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict, giving the teaching in the art, that the method would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

13. If Applicant were able to overcome the rejections under 35 USC 101 and 35 USC 112, first paragraph above, Claims 3-12 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for the claimed method for the diagnosis of leaky TJ junction in the esophageal mucosa, does not reasonably provide enablement for the diagnosis of a precancerous condition of esophageal mucosa. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of diagnosing a precancerous condition of esophageal mucosa, Barrett esophageal condition, in a patient comprising the steps of administering to the patient at least one signature carbohydrate, said patient not having ulcerative disease of the gastrointestinal tract nor bleeding therefore, collecting the urine and measuring for the levels of the carbohydrate, wherein the sugar is mannitol or sucrose wherein an increase in the urine levels of the carbohydrate in the urine of said patient, compared to normal control, is indicative of the precancerous condition, further comprising obtaining a tissue sample from the esophageal mucosa and examining tight junction leakiness of said tissue sample and comparing the TJ leakiness of said tissue sample with that from a control tissue sample wherein an increase in the TJ leakiness of said tissue sample from said patient is indicative of the precancerous condition, wherein the TJ leakiness is correlated with altered expression levels of a protein selected from the group of alpha Pkc, ZO-1, is correlated with reduced phosphorylation state of occludin.

The specification teaches that the present invention relates to methods of early diagnosis of precancerous conditions in a mammal wherein a biological sample is obtained from a gastrointestinal site to detect the presence of a backleak of signature carbohydrates indicating tight junctional leakiness at an early stage of a precancerous condition (p. 1, lines 14-20). Research has indicated that the tight junctional seal surrounding each epithelial cell in an epithelial tissue is compromised in the process of tumor formation and the physiological implications of this

leakiness is that it will compromise the barrier function of the entire epithelial tissue (p. 1, lines 25-34). Precancerous epithelial tight junctions will allow for diffusion of proteins and sugars of the esophagus into the bloodstream (p. 2, lines 5-7). The term "precancerous" as broadly claimed includes conditions of genetic predisposition to cancer, conditions wherein no damage has been done to the esophageal mucosa, conditions wherein there is no leaky TJ. The specification further teaches that tight junctional leakiness in the vicinity of these proteins will allow for their chronic leak into the bloodstream, raising their level in serum. Therefore salivary amylase levels in serum have important diagnostic predictive value for esophageal and gastric precancerous conditions, specifically Barrett's Esophagus, atrophic gastritis and H. Pylori infection (p. 3, lines 9-20). The specification further teaches that sucrose is an excellent marker for ulceration-type leakiness in the upper GI tract because it is normally completely broken down on the duodenal microvilli and is normally completely absent from the bloodstream. When there is a defect in the gastric barrier which would enable undegraded sucrose to diffuse into the bloodstream the sucrose it can be subsequently quantitated in blood and then in urine (p. 14, lines 17-25). The specification exemplifies a prophetic experiment to demonstrate the leakage of luminal salivary amylase and sucrose across the GI barrier in precancerous states in humans (para bridging pages 5-6). The specification describes a prophetic experimental design for the demonstration of the leakage of luminal salivary proteins across the GI barrier in precancerous states in humans. The specification clearly states and emphasizes that "it is necessary to **functionally** (emphasis added) verify TJ leakiness in upper GI

precancerous states in humans and to determine if proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where a cancerous or precancerous lesion exists. This forms the basis of a noninvasive early detection system for upper GI cancer" (p. 13, lines 17-22). The specification further teaches a prophetic example, wherein it is taught how to determine whether leakage of proteins normally sequestered in the lumen of the upper GI tract can cross the GI barrier at sites where precancerous lesion exists (pages 13-15).

One cannot extrapolate the teaching of the specification to the scope of the claims as the specification does not define the term "precancerous". Although Barrett's esophagus is known to predispose some patients to malignancy, not all of the patients with Barrett's esophagus develop adenocarcinoma. Achkar et al (Am. J. Gastroenterology, 1988, 83/3 (291-294) report that the incidence of cancer development after a one year follow-up of 62 patients with Barrett's esophagus was 0.6%, see abstract). The claims, however, are drawn to the diagnosis of a precancerous condition, but the specification does not teach how to determine which of the patients who have, for example, Barrett's esophagus in actuality have a precancerous condition. Further, the claims as written are drawn to patients who, as broadly, claimed include genetic predisposition to cancer of the esophageal mucosa, conditions wherein no damage has been done to the esophageal mucosa, conditions wherein no leaky TJ would be expected. Since it is clear that the hypothesis upon which the invention is based requires that esophageal mucosa epithelial cells have leaky TJ in order to be able to detect anomalous carbohydrate in urine, one would not expect, nor could one predict that the claimed method would be successful in

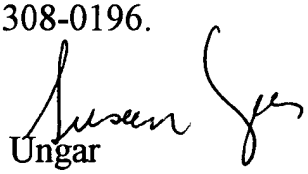
diagnosing the broadly claimed precancerous condition in the absence of the critical leaky TJ. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict, giving the teaching in the art, that the method would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

16 If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Susan Ungar
Primary Patent Examiner
June 4, 2003